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PRENATAL DES EXPOSURE AND SELF-REPORTED IMMUNE-RELATED DISEASES

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ABSTRACT

Objective: To compare self-reports of immune-related diseases in DES daughters and controls. Prenatal exposure to diethylstilbestrol (DES) has been associated with several malformations in the lower genital tract, a higher prevalence of adenosis, and increased risk of clear cell adenocarcinoma, and estrogen-dependent tumors. Lately, reports have been published indicating a link between DES exposure and alterations in the immune system. The present study focuses on the possible clinical consequences of an affected immune system. **Study design:** DES daughters ($N = 170$) and control women ($N = 123$) completed questionnaires containing lists of immune related diseases, specified into three categories (i) allergies, (ii) auto-immune disorders, and (iii) infectious diseases. **Results:** DES daughters reported significantly more disease conditions than the controls. Analyses for separate disease categories (allergies, auto-immune disorders, infectious disease), yielded a statistical significant difference only for infectious disease. Within this last category, two infectious diseases yielded highly significant differences: bladder infection and measles. **Conclusion:** The present findings suggest that DES daughters are at higher risk to develop immune-related disease states.

Keywords: prenatal DES exposure, immunity, self-reported health status

1. Introduction

Prenatal exposure to DES has been demonstrated to be teratogenic and carcinogenic. It is associated with several malformations in the lower genital tract, including vaginal adenosis, ectopic columnar epithelium in the vagina, and a variety of anatomic deviations such as cervical collars and hoods, pseudopolyps of the cervix and cockscomb cervix (1-5). Exposure to large doses has been found to be related with a higher prevalence of adenosis. As the affected girls mature, the adenosis and cervical ectopy may be replaced by squamous metaplasia. In addition, there is evidence that the tubo-endometrial glands of vaginal adenosis may promote the onset of clear cell adenocarcinoma. Recent studies (6,7) have demonstrated increased risks of estrogen-dependent tumors, such as breast, vaginal, and cervical carcinoma in DES daughters and prostate and testicular carcinoma in DES sons. Recent animal research has further yielded evidence that DES exposure may also stimulate the development of prolactinomas (8).

In addition to the increased risk of a variety of somatic problems, DES daughters have been shown to be more vulnerable for mental disorders. For example, Vessey and coworkers (9) have demonstrated that even individuals unaware of their DES exposure were more likely to suffer from anxiety and depressive symptoms. Other studies have substantiated this picture, yielding evidence of increased risk of depression, diminished well-being, and more problems with relationships and sexuality in DES-exposed women than in control women. DES exposure is associated with a continuously ongoing source of worries concerning one's own health risks, pregnancy outcome, and the possible effects on one's offspring. Moreover, there is evidence that there is a greater proportion of left handers among prenatally DES-exposed individuals, possibly reflecting the influence of DES on the developing central nervous system (10, 11).

More recently, the attention of researchers has further focussed on endocrine and immunological abnormalities in DES daughters. Assies and associates (12) have provided some preliminary data indicating that these women are at increased risk for the development of hyperprolactinemia, associated with menstrual disorders, infertility, and primary hypothyroidism. Moreover, elevated plasma testosterone levels were detected in 40% of the subjects. In addition, Assies (13) and Wingard and Turiel (14) have reported on DES-related prolactinomas. Since both estrogens and prolactin are known to modulate immunological responses, it may be speculated that these women may have altered immune system responses, potentially leading to with a wide variety of immune-related diseases. Indeed several lines of evidence - experimental as well as clinical - indicate a link between DES exposure and alterations in immune system responses. Perinatal DES treatment has shown irreversible impairments in the immune system (15, 16). In animal studies, the main effects of DES consisted of a decreased number of T cells - particularly CD4 "helper" cells - and a reduced number of natural killer (NK) cells. In addition, reduced delayed cutaneous hypersensitivity reactions, graft versus host reactions, lymphocyte proliferative responses to T and B cell mitogens, and diminished antibody production were observed. In old animals, tumors of the

genital tract and mammary gland developed (17).

Studies with small samples of DES daughters have also suggested functional alterations in NK cells and a hyper-responsive immune system (18, 19). This would be consistent with the known effects of changes in prolactin level on lymphocyte proliferative response. For example, the administration of exogenous prolactin is associated with significant increments in lymphocyte proliferative response as well as with abolishment of the effects of immunosuppressive drugs. As would be expected, similar effects were observed with the administration of dopamine antagonists, such as the anti-psychotic drug perphenazine -- since dopamine normally inhibits prolactin release at the level of the pituitary. In line with these findings, decreased prolactin level associated with bromocriptine treatment (a dopamine receptor agonist) as well as treatment with cysteamine (a dithiol reducing agent inactivating prolactin) both demonstrated decrements in lymphocyte proliferative response. Further, bromocriptine administration has been associated with increased mortality after a *Listeria* challenge, and the use of anti-psychotic drugs has been suggested to account for studies showing that schizophrenics had a longer life span than the general population. Until now, little attention has been paid to the prevalence of immune system-related diseases including allergies and hypersensitivity reactions, autoimmune disorders, and infectious diseases. Noller and associates have found that autoimmune diseases occur more frequently (about a twofold increase) in women with prenatal DES exposure compared with controls. Corresponding findings have been reported by Wingard and Turiel (14), who compared the results of the 1985 National Health Interview Survey and other population based studies on general health status among mothers, daughters, and sons exposed to DES. Asthma, arthritis, lupus, and diabetes mellitus were reported more frequently among the persons with DES exposure. In addition, the number of reported colds, flu, and respiratory tract conditions proved to be three times as high as control groups. Noller (20) found three infectious conditions differing between the exposed and control group. *Candida* infections and otitis media were more often reported by exposed women, which this author attributes to reporting bias. Surprisingly, kidney infection was found to occur more frequently among controls than among cases. Although one should always be aware of the bias toward pathology in samples participating in this kind of research, these data are nevertheless provocative and warrant further research in this area.

In the present study, the focus is also on self-reports of immune-related diseases. DES daughters and control women were asked to indicate whether they suffer from or - especially in the case of specific (childhood) infectious diseases - had suffered from diseases in which an important role of the immune system may be assumed. It is expected that the DES group would demonstrate a higher prevalence of these diseases.

2. Methods

Subjects. Participants were 179 women who had been prenatally exposed to DES and who were

registered in the Dutch DES Action Center in Utrecht, The Netherlands (age range 19 - 46; $M = 30.0$, $SD = 6.1$). Initially, 500 members of the DES Action Center were randomly selected and invited to participate. Omitting individuals not meeting study inclusion criteria (e.g., mothers, sons, the mentally retarded) and refusals, 208 questionnaires were sent out by mail -- yielding a response rate of 82%.

The control group consisted of 123 women who were acquaintances of the cases in the same age range ($M = 32.0$; $SD = 6.0$) and who had no known history of prenatal DES exposure.

Measures. A list of diseases of the DES-exposed consisted of three categories: (1) allergies (e.g., hay fever, hives, contact allergies), (2) autoimmune disorders (e.g., diabetes, multiple sclerosis, rheumatoid arthritis), and (3) infectious diseases (e.g., measles, infectious mononucleosis, bladder infection) (see Table 1). Comparisons were made for each individual disease and for the summed occurrences over each category.

3. Results

Table 1a-c summarizes the disease prevalence rates in DES daughters and controls. In Table 2, the mean number of diseases within each category is presented. With the exception of infantile eczema and whooping cough, DES daughters report as many, but more often, a higher prevalence of diseases than the control group. Levels of statistical significance (Yates-corrected chi-squares) were only reached for measles and bladder infection. In addition, the total number of reported infectious diseases was significantly higher in the DES group.

4. Discussion

The present study represents only a preliminary report of possible effects of prenatal DES exposure in women on the later occurrence of immune-related disorders. As expected DES daughters reported significantly more illnesses than the controls. This picture emerged for every disease category, but reached statistical significance only for infectious diseases. A more detailed look at the data revealed that two infectious diseases yielded highly significant differences: bladder infection and measles. Although the increased susceptibility to bladder infections may at least partly be attributed to the well known malformations and developmental abnormalities of the urogenital tract in DES daughters, it cannot be excluded that local immunological changes in the bladder mucosa and its transitional epithelium also play a role, as is known for the cervical mucosa and its columnar epithelium in the etiology of squamous cell carcinoma of the cervix (21) -- another condition associated with DES exposure.

Sex steroids are known to influence human immune mechanisms. Chronic infection with

Candida albicans is common in women, especially during pregnancy. Mathur and coworkers (22) showed the production of antibodies to be specifically influenced by sex steroid hormones -- being enhanced by progesterone and estradiol at low levels, but depressed by estradiol at high levels. Very importantly, DES injection into rats with normal urinary tracts was shown to induce squamous metaplasia of the transitional epithelium of the bladder, distal and proximal ureters, varying degrees of hydronephrosis and an increased susceptibility to renal parenchymal infection (23). In contrast, it is far more difficult to speculate about the mechanisms responsible for the dramatic differences in measles infection rates. It is tempting to hypothesize that this increased susceptibility to measles reflects the hypothesized gender-specific effect of DES on the immune system, since boys, indeed, are known to be more susceptible to measles than non-DES-exposed girls. However, at the subjective level no evidence supporting a masculinizing effect of DES has been found in the present sample (24).

Another interesting aspect of the increased prevalence of measles in the DES group is related to the recent available evidence that there is an association between being infected by measles and viral-induced autoimmune diseases, including multiple sclerosis and -- possibly -- schizophrenia. Of note here is that paramyxoviruses, such as measles virus, have a known predilection to invade the CNS, resulting in CNS diseases -- i.e., subacute sclerosing panencephalitis in the case of measles virus (25).

Although the differences failed to reach statistical significance, it nevertheless may be notable that thyroid problems, multiple sclerosis and diabetes indeed did show a higher prevalence in the DES group -- in particular when expressed as relative risks. In Noller's study (26), the overall prevalence of any autoimmune disease was increased, but one disease in particular, Hashimoto's thyroiditis, occurred significantly more frequently among exposed women. The presence of vaginal epithelial changes (adenosis, metaplasia) is, in general, a marker for being exposed to higher DES doses. Women with vaginal epithelial changes had nearly 50% more autoimmune disease than DES exposed women without vaginal changes.

The present finding thus once more supports the hypothesis that prenatal DES exposure increases the risk of developing immune-related disorders. Whereas previous studies focused on allergic conditions and autoimmune disorders, the present study extends these findings to the realm of infectious diseases. In addition, there is growing interest in the consequences of DES exposure for the immune system. Animal work has yielded evidence of lifelong immunosuppression, as reflected in a reduced number of CD4 "T helper" cells and NK cells. Mice with neonatal exposure show impaired B cell response and a reduced ability to resist tumors. A limited number of human studies suggest a hyper-reactive immune response in DES daughters and indications for possible functional alterations in NK cells of clinical significance, which would be particularly important to viral infections and tumor development.

Whereas it is already established from a biomedical point of view that prenatally DES-

exposed individuals show an increased risk of immune-related diseases, looking at this issue from a psychoneuroimmunological perspective expands the potential risk for immune-related diseases. The picture that emerges is that these women showed increased levels of distress, as reflected in elevated scores on the Hopkins Symptom Checklist. The combination of a state of distress and an already compromised immune system may facilitate the onset of clinical symptoms, as occurs in HIV-1 infection (27, 28). This situation may be exacerbated by a weakened family process in which a chronic family physical health stressor has been imposed -- the shared susceptibility to diseases associated with DES exposure. Further, if this stressor is met with passive rather than active coping strategies and with a lack of outside social support, this disposition toward high distress may be potentiated over time. An intriguing question, then, is to what extent psychosocial interventions might play a role in preventing the aforementioned process from occurring and, as a consequence, prevent or delay the onset of immune-related diseases in individuals with in utero exposure to DES.

It should be emphasized that this study demonstrates some serious limitations. It is a selective sample, because it includes only DES daughters who are involved in the organization. We are also aware of the limitations of this and many other studies, where there is a lack of detailed information about the actual DES dosage and the duration of exposure. Nevertheless, the results are suggestive and extend the data from prior work, which also showed an increased prevalence of a variety of immune-related diseases following in utero exposure to DES. Given these findings, we would like to stress the importance of immunoendocrinological studies of DES daughters, in order to obtain a better insight into mechanisms that may be responsible for the greater disease susceptibility. We would emphasize that DES daughters who are very distressed and concerned about their future health, have the right to be taken seriously by health care workers and, when needed, to get extra attention and support. This is not only a task for the DES Action Centers, but also for general practitioners and gynecologists as well.

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- Table 1(a-c). Self-reported prevalences (percentages) of diseases in DES daughters and controls. In addition, Yates corrected chi-squares are reported.

A. Allergies	Controls N = 123	DES N = 170	Chi-sq	p
1. hay fever	16	20	0.77	ns
2. chronic rhinitis	12	16	0.78	ns
3. asthma	9	11	0.01	ns

4. hives	7	12	1.37	ns	
5. eczema		24	25	0.00	ns
6. contact allergy (rubber, cosmetics, etc)		22	32	2.74	.09
7. hypersensitivity to food or medication	20	23	0.01	ns	
8. hypersensitivity other e.g., cat hairs, sting of bees, etc)		20	29	2.60	.11
9. infantile eczema		9	5	1.77	ns

B. Autoimmune disorders

1. thyroid problems		3	8	1.07	ns
2. rheumatoid disorders	4	4	0.00	ns	
3. multiple sclerosis		0	6	2.66	.10
4. diabetes		1	3	0.63	ns
5. psoriasis		4	4	0.00	ns

C. Infectious disease

1. influenza (past 2 years)		57	62	0.54	ns
2. mumps		42	46	0.45	ns
3. rubella		38	43	0.62	ns
4. whooping cough		11	8	0.54	ns
5. measles		49	69	11.90	<.001
6. jaundice		7	8	0.00	ns
7. chicken pox		60	63	0.27	ns
8. herpes zoster	5	8	0.42	ns	
9. herpes simplex - 1		27	27	0.00	ns
10. herpes simplex - 2		4	5	0.00	ns
11. infectious mononucleosis		9	9	0.00	ns
12. (chronic) bronchitis	14	21	2.61	ns	
13. pneumonia		10	15	1.27	ns
14. bladder infection		35	50	5.54	<.02
15. otitis media	28	34	1.08	ns	
16. fungal infections		49	51	0.09	ns
17. sexually transmitted diseases		5	6	0.07	ns

Table 2. Summary of the mean number of diseases reported by DES daughters and Controls.

		Controls	DES	t-value	p
Total number of reported diseases		8.23	9.74	2.96	<.01
Total allergies		1.66	2.03	1.44	ns
Total autoimmune disorders		0.10	0.19	1.22	ns
Total infectious disease	6.52	7.52	2.95	<.01	